Evaluating Compounds with Influence in the Gut

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Take-Home Message

There are a variety of situations in an animal's life-cycle that challenges her ability to maintain homeostasis. Most are familiar with the marked metabolic adaptations that female farm animals utilize to copiously synthesize milk following parturition and unfortunately this is often referred to as "metabolic stress". In addition to the metabolic challenges and potential for "nutritional stress" during the transition period, animals could encounter adverse weather (cold and/or heat stress) and other environmental stressors like overcrowding, inadequate ventilation, poor footing, uncomfortable stalls, poor management of grouping and pen movement, inadequate access to water, contaminated water, and rough handling. The metabolic consequences of heat stress have been well-characterized and increasing evidence implicates a compromised intestinal barrier function as one of the key origins of heat stress-induced decreased productivity. Interestingly, we have now demonstrated that reduced feed intake (a conserved response to heat stress) also compromises intestinal integrity in both thermal neutral monogastrics and ruminants. Thus, stressors that physically prevent ad libitum feed intake or cause voluntarily reductions in feed take may share a common mechanism(s). Thus, identifying flexible nutritional strategies to mitigate stress-induced intestinal health issues is important.

Introduction

One common response to most "stressors" is a reduction (either voluntarily or involuntary) in feed intake. Further, we have now demonstrated that the consequence (decreased nutrient intake) of stress negatively impacts intestinal barrier function. Because of its highlighted importance in the last three decades, most are familiar with the metabolic "stress" that occurs following calving. Stress is in quotation marks because, in our opinion, the metabolic changes occurring pre- and post-calving are normal homeorhetic adaptations that all female animals utilize to support milk production. Metabolic maladaptation to lactation results in ketosis and this is in part either caused by inadequate feed intake or causes reduced feed intake. Regardless, although heavily researched for the last three decades, the specific etiology and cause of transition period ketosis remains elusive as it is unclear why a small percentage of cows are susceptible (or predisposed?) to metabolic imbalances following calving. In contrast, the metabolic consequences of heat stress are now becoming increasingly realized and we now have ample evidence to suggest that the origin of heat-compromised productivity is at the intestinal level. Because of space constraints, the rest of this paper will concentrate on the effects of heat stress and nutritional strategies that may help strengthen intestinal integrity. These strategies will presumably benefit any stress that damages the intestinal epithelium (rumen or hind gut acidosis) or causes reduced feed intake (which indirectly endangers intestinal barrier function).

1.0 Heat Stress

1.1 Economic Impact: Heat stress negatively impacts a variety of dairy production parameters including milk yield, milk quality and composition, rumen health, growth and reproduction, and is a significant financial burden (~$900 million/year for dairy, and > $300 million/year in beef and swine in the U.S. alone; St. Pierre et al., 2003; Pollman, 2010). When the ambient temperature and other environmental conditions create a situation that is either below or above the respective threshold values, efficiency is compromised because nutrients are diverted to maintain euthermia as preserving a safe body temperature becomes the highest priority, and product synthesis (milk, meat, etc.) is deemphasized. Advances in management (i.e. cooling systems; VanBaale et al., 2005) and nutritional strategies (West, 2003) have partially alleviated the negative impacts of HS on cattle, but productivity continues to decline during the summer. The detrimental effects of HS on animal welfare and production will likely become more of an issue in the future if the earth's climate continues to warm as predicted (IPCC 2007) and some models forecast extreme summer conditions in most U.S. animal producing areas (Luber and McGeehin, 2008). A 2006 California heat wave purportedly resulted in the death of more than 30,000 dairy cows (CDFA, 2006) and a recent heat wave in Iowa killed at least 4,000 head of beef cattle (Drovers Cattle Network, 2011). Furthermore, almost 50% of Canadian summer days are environmentally stressful to dairy cows (Ominski et al., 2002). This illustrates that most geographical locales, including temperate and northern climates, are susceptible to extreme and lethal heat. Thus, for a variety of aforementioned reasons, there is an urgent need to have a better understanding of how HS alters nutrient utilization and ultimately reduces animal productivity. Defining the biology of how HS jeopardizes animal performance is critical in developing approaches (genetic, managerial, nutritional and pharmaceutical) to ameliorate current production issues and improve animal well-being and performance. This would help secure the global agricultural economy by ensuring a constant supply of animal products for human consumption.

1.2 Direct and Indirect Effects of Heat Stress: Reduced feed intake during HS is a highly conserved response among species and presumably represents an attempt to decrease metabolic heat production (Baumgard and Rhoads, 2012). It has traditionally been assumed that inadequate feed intake caused by the thermal load was responsible for decreased milk production (Beede and Collier, 1986; West, 2003). However, our recent results challenge this dogma as we have demonstrated disparate slopes in feed intake and milk yield responses to a cyclical heat load pattern (Shwartz et al., 2009). To test this, we employed the use of a thermoneutral pair-fed group in our experiments which allowed us to evaluate thermal stress while eliminating the confounding effects of dissimilar nutrient intake. Our experiments demonstrate that reduced feed intake only explains approximately 35-50% of the decreased milk yield during environmental-induced hyperthermia (Rhoads et al., 2009a; Wheelock et al., 2010; Baumgard et al., 2011). This indicates that HS directly effects nutrient partitioning beyond that expected by reduced feed intake.

1.3 Normal Metabolic Adaptations to Reduced Feed Intake: An appreciation of the physiological and metabolic adjustments to thermoneutral negative energy balance (NEBAL; i.e. underfeeding or during the transition period) is prerequisite to understanding metabolic adaptations occurring with HS. Early lactation dairy cattle enter a unique physiological state during which they are unable to consume enough nutrients to meet maintenance and milk production costs and typically enter NEBAL (Baumgard and Rhoads, 2013). Negative energy balance is associated with a variety of metabolic changes that are implemented to support the dominant physiological condition of lactation (Bauman and Currie, 1980). Marked alterations in both carbohydrate and lipid metabolism ensure partitioning of dietary and tissue derived nutrients towards the mammary gland, and not surprisingly many of these changes are mediated by endogenous

somatotropin which naturally increases during periods of NEBAL. One classic response is a reduction in circulating insulin coupled with a reduction in systemic insulin sensitivity. The reduction in insulin action activates adipose lipolysis, leading to the mobilization of non-esterified fatty acids (NEFA; Bauman and Currie, 1980). Increased circulating NEFA are typical in transitioning cows and represent (along with NEFA derived ketones) a significant source of energy (and precursors for milk fat synthesis) for cows in NEBAL. Postabsorptive carbohydrate metabolism is also altered by reduced insulin action during NEBAL resulting in reduced glucose uptake by systemic tissues (i.e. muscle and adipose). Reduced nutrient uptake coupled with the net release of nutrients (i.e. amino acids and NEFA) by systemic tissues are key homeorhetic (an acclimated response vs. an acute/homeostatic response) mechanisms implemented by cows in NEBAL to support lactation. The thermoneutral cow in NEBAL is metabolically flexible, and can depend upon alternative fuels (NEFA and ketones) to spare glucose. Glucose can then be utilized by the mammary gland to copiously produce milk (Bauman and Currie, 1980).

Well-fed ruminants primarily oxidize acetate (a rumen produced VFA) as a principal energy source. During NEBAL, cattle increase their energy dependency on NEFA. However, despite the fact that heat stressed cows have marked reductions in feed intake and are losing considerable amounts of body weight, they do not mobilize adipose tissue (Rhoads et al., 2009a; Wheelock et al., 2010). Therefore, it appears that heat stressed cattle experience altered post-absorptive metabolism compared to thermoneutral counterparts, even though they are in a similar negative energetic state (Moore et al., 2005; Rhoads et al., 2013). The unusual lack of NEFA response in heat stressed cows is probably in part explained by increased circulating insulin levels (O'Brien et al., 2010; Wheelock et al., 2010), as insulin is a potent anti-lipolytic hormone. Increased circulating insulin during HS is unusual as malnourished animals are in a catabolic state and experience decreased insulin levels. We have recently demonstrated that heat stressed growing pigs undergo similar metabolic adaptations (Pearce et al., 2013a), suggesting that this is a well conserved response vital for the acclimation to HS. Increased insulin action may also explain why heat stressed animals have greater rates of glucose disposal (Wheelock et al., 2010). Therefore, during HS, preventing or blocking adipose mobilization/ breakdown and increasing glucose "burning" is presumably a strategy to minimize metabolic heat production (Baumgard and Rhoads, 2013). The enhanced extra-mammary glucose utilization during HS creates a nutrient trafficking problem with regards to milk yield. The mammary gland requires glucose to synthesize milk lactose which is the primary osmoregulator determining overall milk volume. Therefore, the mammary gland may not receive adequate amounts of glucose resulting in reduced mammary lactose and subsequent milk production. This may be a primary mechanism accounting for additional reductions in milk yield beyond the portion explained by decreased feed intake.

2.0 Leaky Gut: Responsible for the Direct Effects of Heat Stress?

Mechanisms responsible for altered nutrient partitioning during HS are not clear, however, they might be mediated by HS effects on gastrointestinal health and function (Figure 1). The small intestine is one of the first tissues up-regulating heat shock proteins during a thermal load (Flanagan et al., 1995), demonstrating a higher sensitive to heat damage (Kregel, 2002). During heat stress, blood flow is diverted from the viscera to the periphery in an attempt to dissipate heat (Lambert et al., 2002), leading to intestinal hypoxia (Hall et al., 1999). Enterocytes are particularly sensitive to hypoxia and nutrient restriction (Rollwagen et al., 2006), resulting in ATP depletion and increased oxidative and nitrosative stress (Hall et al., 2001). This contributes to tight junction dysfunction, and gross morphological changes that ultimately reduce intestinal barrier function (Lambert et al., 2002; Pearce et al., 2013b). As a result, HS increases the passage of luminal content as lipopolysaccharide (LPS) into the portal and systemic blood (Hall et al., 2001; Pearce et al., 2013b). Further, endotoxemia is common among heat stroke patients

(Leon, 2007) and it is thought to play a central role in heat stroke pathophysiology, as survival increases when intestinal bacterial load is reduced (Bynum et al., 1979) or when plasma LPS is neutralized (Gathiram et al., 1987). It is remarkable how animals suffering from heat stroke or severe endotoxemia share many physiological and metabolic similarities such as an increase in circulating insulin (Lim et al., 2007). Infusing LPS into the mammary gland increased (~2 fold) circulating insulin in lactating cows (Waldron et al., 2006). In addition, we intravenously infused LPS into growing calves and pigs and demonstrated >10 fold increase in circulating insulin (Rhoads et al., 2009b; Stoakes and Baumgard, unpublished). Again, the increase in insulin in both models is energetically difficult to explain as feed intake was severely depressed in both experiments.

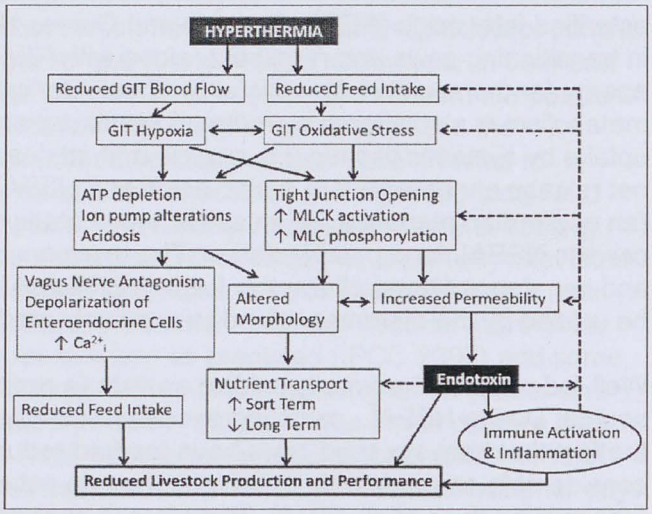

Figure 1. Etiology of heat stress induced leaky gut.

2.1 Intestinal Integrity and Steatohepatitis: Interestingly, a variety of diseases associated with increased intestinal permeability such as heat stress and stroke, Crohn's disease, inflammatory bowel disease, Celiac disease, and alcoholism are often characterized by increased plasma LPS concentrations and an inflammatory acute phase response (Bouchama et al., 1993; Pearce, et al. 2013b; Draper et al., 1983; Parlesak et al., 2000; Ludvigsson et al., 2007). There is increasing evidence that translocation of gut microbiota contributes to hepatic inflammation (Bieghs and Trautwein, 2013) which might impair liver function leading to fat accumulation and ultimately steatohepatitis (Ilan, 2012; Dumas et al., 2006; Solga and Diehl, 2003; Farhadi et al., 2008; Miele et al., 2009). The association between leaky gut and fatty liver is of particular interest in the ruminant animal who is already an inefficient exporter of hepatic lipids. There is reason to believe that similar breakdown of gut integrity may be responsible for hepatic disorders (e.g. fatty liver and ketosis; Figure 2) frequently observed in the transition dairy cow. A transitioning dairy cow undergoes a post-calving diet shift from a mainly forage based to a high concentrate ration. This has the potential to induce rumen acidosis which can compromise the gastrointestinal tract barrier (Khafipour et al., 2009). In addition, calving is a physically stressful event and cytokines released from the damaged reproductive tract may have an impact on the liver's ability to export lipids. Preliminary data has shown an increase in plasma lipopolysaccharide binding protein (LPSBP), an acute phase protein which binds LPS to stimulate an immune response, in cows that required treatment for clinical ketosis compared to healthy transition cows (Nayeri et al., 2012). Nevertheless, the effects of the transition period on the intestinal barrier function

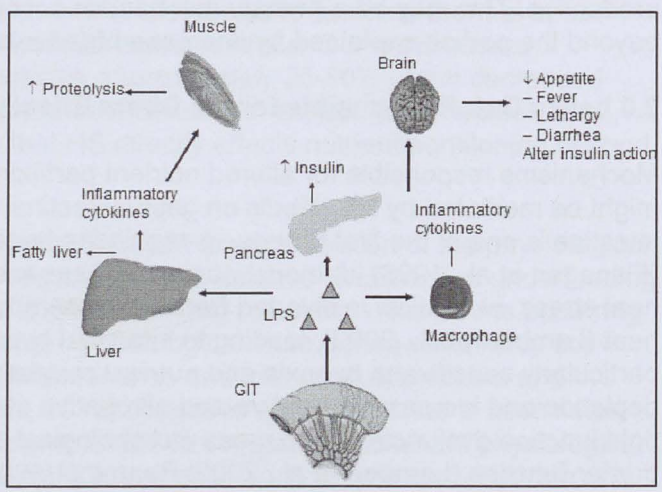

Figure 2. LPS induced metabolic alterations.

and its role in the development of fatty liver and ketosis among other transition disorders remain unknown and require further investigation.

3.0 Strategies to Prevent Leaky Gut

3.1 Bicarbonate: Acidosis may exacerbate intestinal issues (Khafipour et al., 2009) as rumen pH is lowered during the summer months (Mishera et al., 1970). This may be explained by increased respiration rate which decreases blood carbon dioxide (CO_2) and increases the need for the kidney to secrete bicarbonate to maintain a healthy 20 to 1 ratio of bicarbonate to CO_2 in the blood. Increased secretion of bicarbonate by the kidney reduces the amount available to be used in the saliva to buffer rumen pH. In addition, reduced feed intake results in reduced rumination time which is a key stimulator of saliva production. Thus, the increased susceptibility of heat-stressed cattle to rumen acidosis might be prevented by dietary bicarbonate supplementation.

3.2 Glutamine: Glutamine is a conditionally non-essential amino acid as it can be formed from ammonia and glutamate. It is a primary energy source for intestinal cells (Singleton and Wischmeyer, 2006) and supplemental dietary glutamine has demonstrated improvement in intestinal barrier function in malnourished children (Lima et al., 2005). A potential mechanism of action for glutamine's beneficial effects is the enhanced expression of heat-shock protein 70 (Singleton and Wischmeyer, 2006). Glutamine supplementation to high producing thermoneutral cows did not improve milk yield (Metcalf et al., 1996). However, a study by Caroprese and co-workers (2013) demonstrated that during HS, glutamine supplementation improved milk, fat, protein, and casein yields. Caroprese and colleagues also observed improvement in cell mediated immune response which was likely responsible for the observed lower somatic cell count, possibly indicating a role for glutamine in the alleviation of mastitis.

3.3 Zinc: Dietary zinc is essential for normal intestinal barrier function (Alam et al., 1994), and supplemental zinc is beneficial in a variety of animal models and human diseases characterized by increased intestinal permeability (Alam et al., 1994; Zhang and Guo, 2009). We have recently demonstrated that supplemental zinc can partially alleviate the effects HS on intestinal integrity in acute and chronically heat-stressed growing pigs (Sanz-Fernandez et al., 2014; Pearce et al., 2013b). The mechanisms by which zinc improves intestinal integrity are not well-understood, but might include: the up-regulation of tight junction proteins (Zhang and Guo, 2009), a role as antioxidant via induction of metallothioneins (Wang et al., 2013), increasing the expression of antimicrobial substances as β-defensins (Mao et al., 2013) and/or sequestering and neutralizing blood LPS (Thomas et al., 2008).

3.4 Dairy Products: Dietary dairy products (e.g. colostrum and whey protein) have been also demonstrated to improve intestinal health under different types of challenges (Playford et al., 1999 and 2001; Khan et al., 2002; Prosser et al., 2004). Interestingly, dietary dairy products have demonstrated alleviation of HS effects on the intestinal barrier function both *in vivo* (Prosser et al., 2004) and *in vitro* (Marchbank et al., 2011). Once again their mechanisms of action are not well understood but both colostrum and whey protein are rich in antimicrobial proteins (e.g. glucomacropeptides, lactoferrin), immunoglobulins, growth factors (e.g. Transforming Growth Factor-β), and certain amino acids (glutamine, cysteine, and threonine; Krissansen, 2007). Further, dietary dairy products have shown to up-regulation heat-shock protein 70 (Marchbank et al., 2011) and tight junction proteins (mediated by TGF-β; Hering et al., 2011), and increase mucin production (mediated by threonine and cysteine; Sprong et al., 2010); which might explain their beneficial effect on intestinal health.

3.5. Conjugated Linoleic Acid: Inhibiting milk fat synthesis during HS may attenuate or eliminate the negative energy balance. As a result of the extra available energy, synthesis of other milk and milk components may increase (i.e., lactose and protein). In addition to enhancing milk yield, inhibiting milk fat synthesis and thus improving energy balance may improve animal well-being and reproductive success (Bauman et al., 2001). We utilized conjugated linoleic acid (CLA) in an attempt to strategically improve energy balance during HS, but did not detect any noticeable improvement in production variables (Moore et al., 2005).

3.6 Antioxidants: Hypoxia of the small intestine leads to oxidative stress and free radical production (Hall et al., 1999). In addition, intestinal inflammation leads to loss of antioxidant capacity (Buffinton and Doe, 1995b). Therefore, antioxidant supplementation such as selenium and vitamins A, E, and C could potential mitigate oxidative stress.

Vitamin A can mitigate the effects of induced mucosal damage (Elli et al., 2009) and deficiency can have negative effects on immunity and integrity in the gut (Yang et al., 2011; Thurnham et al., 2000). This was the case of vitamin A-deficient beef calves that suffered reduced intestinal integrity and were more susceptible to a secondary E. coli infection (He, et al., 2012). Dietary vitamin A has the potential to improve weight gain and feed efficiency in HS broilers and this effect was amplified when vitamin A was combined with zinc (Kucuk et al., 2003). In addition, cows supplemented with β-carotene during hot months had increased milk yield and pregnancy rates (Aréchiga et al., 1998).

Vitamin E supplementation has reduced gut bacterial translocation and increased survival in radiation induced intestinal injury (Singh et al., 2012). Supplementation also increases vitamin A serum concentrations, suggesting a protective role for vitamin E on vitamin status (Sahin et al., 2002b). Sahin and coworkers (2002a) also demonstrated improved production performance in Japanese quails supplemented with vitamin C and E during HS. Dairy cows administered 3000 IU of vitamin E during two consecutive summers had similar pregnancy rates compared to controls (Ealy et al., 1994), however little research has examined its effects on production and immune status in dairy cows.

Vitamin C is decreased in inflammatory bowel disease patients (Buffinton and Doe, 1995a) as well as heat stressed lactating cows (Padilla and Matsuia, 2006). Supplementation has demonstrated positive effects during HS by reducing tocopheroxyl radicals back to the active form of vitamin E (Sahin, 2002b).

Selenium is part of selenoproteins such as glutathione peroxidase, which is a major free radical scavenger system in the cell (Loeb et al., 1988). Selenoproteins also play an important role in cell growth as deficiency has been linked to DNA damage and poor cell cycle control (Rao et al., 2001) which may be pertinent to intestinal integrity due to high enterocyte turnover rate. In patients with celiac disease, characterized by small intestine damage, selenium deficiency is a risk factor due to poor absorption which can lead to increased reactive oxygen species and inflammation (Stazi and Trinti, 2008; Barrett et al., 2013). Supplementation with selenium has the potential to reduce lipid peroxidation and epithelial damage to intestinal mucosa, and prevent bacterial translocation (Baldwin and Wiley, 2002; Oztürk et al., 2002). Sheep injected with selenium during HS lost less weight compared to their HS control counterparts (Alhidary et al., 2012).

Many of the antioxidant compounds listed above have synergistic effects with one another or with minerals like zinc (Kucuk et al., 2003; Sahin et al., 2002a, 2002b). Research demonstrating effects of supplemental antioxidant on production parameters during HS is scarce and further

research is needed to allow for the development of supplementation recommendations, particularly in ruminants.

Table 1. Potential nutritional strategies to ameliorate intestinal permeability.

Supplement	Presumed Mechanism of Action
Bicarbonate	Acidosis prevention
Glutamine	↑ intestine integrity
Zinc	↑ intestine integrity
Dairy Products	↑ intestine integrity
Vitamin A	Antioxidant
Vitamin C	Antioxidant
Vitamin E	Antioxidant
Selenium	Antioxidant
Dexamethasone	↑ intestine integrity
Betaine	Osmotic regulation; CH_3 donor
Conjugated Linoleic Acid	↑ Energy balance
Chromium	↑ Feed Intake
Yeast, Yeast Extract/DFM	Acidosis prevention & ↑ feed intake
Ionophores	Acidosis prevention
β-glucan	Immune modulation
Mannanoligosaccharide	↑ intestine integrity

3.7 Dexamethasone: Dexamethasone is a synthetic corticosteroid with anti-endotoxic and anti-inflammatory properties. Previous research has demonstrated a marked increase in corticosteroids in response to HS (Collier et al., 1982; Baumgard and Rhoads, 2013). Dexamethasone prevented the increase in plasma aspartate transaminase and alanine aminotransferase (both markers of hepatic health), IL-6 and LPS in a rat model of heat stroke, probably by blocking endotoxemia (Lim et al., 2007). Also in a heat stroke model, primates injected with corticosteroid had reduced endotoxemia as well as an increased survival rate (Gathiram et al., 1988a, 1988b). Further research is needed within the livestock industry to explore potential pharmacological roles of dexamethasone in heat stress abatement practices.

3.8 Betaine: Betaine, also known as trimethylglycine, is an osmotic regulator and methyl donor which may exhibit several beneficial effects in heat-stressed animals including the potential to protect against osmotic stress by decreasing sodium potassium pump activity (Cronje, 2007). Betain supplementation improves intestinal integrity in both healthy and coccidian infected birds (Kettunen et al., 2001). In addition, betaine ameliorated the effects of HS on weight gain, immunity and body temperature indices in rabbits (Hassan et al., 2011). Supplemented thermoneutral mid-lactation dairy cows experienced an increase in milk yield, a decrease in milk protein percent, and altered milk fatty acid profile (Peterson et al., 2012). However, no differences were observed in milk production parameters in HS cows (Hall et al., 2012). Lack of sufficient evidence in support of or against betaine's role in HS alleviation warrants the need for further investigation.

3.9 Chromium: Chromium is a micronutrient that facilitates insulin action on glucose, lipid, and protein metabolism. As glucose utilization predominates during heat stress, chromium supplementation may improve thermal tolerance or production in heat-stressed animals. However, one consistent effect of chromium supplementation during heat stress is an increase

in feed intake (Al-Saiady et al., 2004; An-Qiang et al., 2009) and this may be as important aspect of how it appears to ameliorate the negative consequences of heat stress.

3.10 Fermentation modifiers: Because the heat-stressed cow has an increased need for glucose, dietary strategies that can safely increase rumen propionate production is likely a good strategy. The word safely is emphasized as although additional grain or feed processing can obviously increase propionate production these methods likely also decrease rumen pH and the heat-stressed cows is already prone to rumen acidosis for a variety of reasons (Baumgard and Rhoads, 2012, 2013). Consequently, supplements like monensin and other ionophores are an effective method of increasing the post-absorptive carbohydrate status and some evidence suggest that feeding Rumensin actually increases rumen pH via increasing meal frequency.

4.0 Management Strategies

Despite increased efforts to combat HS through nutritional strategies, cooling technology and management practices still represent the main approach to relieve HS. Providing shade, ventilation, and cooling as well as reducing walking distance can be strategies implemented to reduce the harmful effects of HS. Increasing milking frequency is strategy that has not been thoroughly evaluated during HS, but is a well-described lactogenic stimulant during thermal neutral conditions (Fitzgerald et al., 2007). Controlling the timing of feeding is also beneficial, as early morning and late night feeding helps to push the peak heat of fermentation to cooler parts of the day. Pushing up feed often so cows consume several small meals instead of a few large meals will aid in acidosis prevention and reduce steep increases in metabolic heat caused by consuming a large meal. Stressors of any kind (i.e. vaccinations) should be avoided during hotter parts of the day as the combination of HS and handling stress is unfavorable. Administration of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided as they may exacerbate gastrointestinal integrity issues.

5.0 Conclusion

High ambient temperatures have a negative effect on animal health and performance, costing billions of dollars in losses to global animal agriculture. Gut integrity is compromised by HS and the resultant systemic inflammation might partially explain its negative effects on production. Nutrition is an example of an easily adjustable tactic to ameliorate the detrimental effects of environmental hyperthermia. For instance, heat-stressed animals shift energy metabolism toward carbohydrate usage and reduce lipid oxidation. Therefore, diets or nutritional supplements promoting glucose production (i.e. ionophores) and utilization may be useful. In addition, intestinal health improvement via dietary supplementation might be advantageous. Finally, cooling management practices such as shade, evaporative cooling, and strategic timing of farm activities aid in the mitigation of the adverse effects of HS. Even in today's most well managed dairies, HS remains a problem. In order to resolve current HS production issues and develop better mitigation strategies, a better understanding of the biology and mechanisms of how HS threatens animal health is essential.

**Parts of this proceedings paper were adapted from the 74th Minnesota Nutrition Conference proceedings, September 17-18, 2013 in Prior Lake, MN, and the 2014 Western Canadian Nutrition Conference.*

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